

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
4 March 2004 (04.03.2004)

PCT

(10) International Publication Number
WO 2004/018450 A1

- (51) International Patent Classification⁷: **C07D 401/04**, 405/14, A61K 31/50
- (72) Inventor; and
(75) Inventor/Applicant (for US only): **STERK, Geert, Jan** [NL/NL]; Stadhouderslaan 38, NL-3583 JJ Utrecht (NL).
- (21) International Application Number:
PCT/EP2003/008676
- (74) Agent: **WILD, Robert**; Altana Pharma AG, Byk-Gulden-Strasse 2, 78467 Konstanz (DE).
- (22) International Filing Date: 6 August 2003 (06.08.2003)
- (81) Designated States (national): AE, AL, AU, BA, BR, CA, CN, CO, DZ, EC, GE, HR, ID, IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL, SG, TN, UA, US, VN, YU, ZA, ZW.
- (25) Filing Language: English
- (26) Publication Language: English
- (84) Designated States (regional): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).
- (30) Priority Data:
02017978.4 10 August 2002 (10.08.2002) EP
- (71) Applicant (for all designated States except US): **ALTANA PHARMA AG** [DE/DE]; Byk-Gulden-Str. 2, 78467 Konstanz (DE).
- (72) Inventors (for AE, AL, AM, AT, AU, AZ, BA, BE, BG, BR, BY, CH, CN, CO, CY, CZ, DE, DK, DZ, EC, EE, ES, FI, FR, GB, GE, GR, HR, HU, ID, IE, IL, IN, IS, IT, JP, KG, KR, KZ, LT, LU, LV, MA, MC, MD, MK, MX, NL, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, UA, VN, YU, ZA, ZW only): **HATZELMANN, Armin**; Alter Wall 3, 78467 Konstanz (DE). **BARSIG, Johannes**; Bleichenweg 11, 78467 Konstanz (DE). **MARX, Degenhard**; Obere Reute 15, 78345 Moos (DE). **KLEY, Hans-Peter**; Im Weinberg 3b, 78476 Allensbach (DE). **BRUNDEL, Paulus, Johannes, Gaurerius**; v. Brakelstraat 51 A, NL-3814 RJ Amersfoort (NL). **CHRISTIAANS, Johannes, A., M.**; Zevenwouden 233, NL-3524 CR Utrecht (NL). **MENGE, Wiro, M., P., B.**; Pontanuslaan 11, NL-6821 HM Arnhem (NL).
- Declarations under Rule 4.17:**
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AL, AU, BA, BR, CA, CN, CO, DZ, EC, GE, HR, ID, IL, IN, IS, JP, KR, LT, LV, MA, MK, MX, NO, NZ, PH, PL, SG, TN, UA, VN, YU, ZA, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR)
 - as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
 - of inventorship (Rule 4.17(iv)) for US only
- Published:**
- with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PIPERIDINE-N-OXIDE-DERIVATIVES

(57) Abstract: The compounds of a certain formula (1), in which the given substituents have the meanings as indicated in the description, are novel effective PDE4 inhibitors.



WO 2004/018450 A1

PIPERIDINE-N-OXIDE-DERIVATIVES**Field of application of the invention**

The invention relates to novel piperidine-N-oxide-derivatives, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

Known technical background

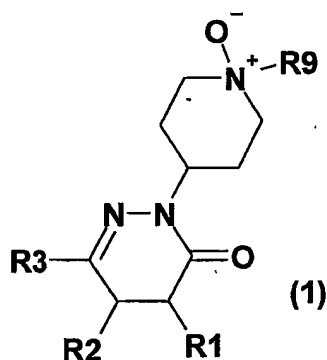
International Patent Applications WO98/31674 (= USP 6,103,718), WO99/31071, WO99/31090, WO99/47505 (= USP 6,255,303), WO01/19818, WO01/30766, WO01/30777, WO01/94319, WO02/064584, WO02/085885 and WO02/085906 disclose phthalazinone derivatives having PDE4 inhibitory properties. In the International Patent Application WO94/12461 and in the European Patent Application EP 0 763 534 3-aryl-pyridazin-6-one and arylalkyl-diazinone derivatives are described as selective PDE4 inhibitors. International Patent Application WO93/07146 (= USP 5,716,954) discloses benzo and pyrido pyridazinone and pyridazinthione compounds with PDE4 inhibiting activity.

In the Journal of Medicinal Chemistry, Vol. 33, No. 6, 1990, pp. 1735-1741 1,4-Bis(3-oxo-2,3-dihydropyridazin-6-yl)benzene derivatives are described as potent phosphodiesterase inhibitors and inodilators. In the Journal of Medicinal Chemistry Vol. 45 No.12, 2002, pp. 2520-2525, 2526-2533 and in Vol. 44, No. 16, 2001, pp. 2511-2522 and pp. 2523-2535 phthalazinone derivatives are described as selective PDE4 inhibitors.

Description of the invention

It has now been found that the piperidine-N-oxide-derivatives, which are described in greater details below, have surprising and particularly advantageous properties.

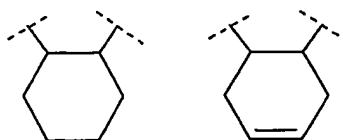
The invention thus relates to compounds of formula 1



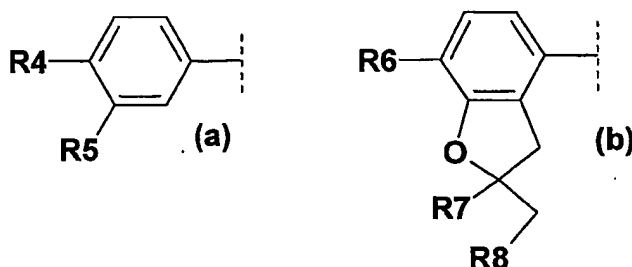
in which

- 2 -

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is $-(CH_2)_m-S(O)_2-R10$, $-(CH_2)_n-C(O)-R11$ or $-(CH_2)_p-Z-(CH_2)_q-R14$,

R10 is $-N(R12)R13$,

R11 is $-N(R12)R13$,

R12 and R13 are independent from each other hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkylmethyl, or R12 and R13 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl- or a 1-hexahydroazepinylring,

Z represents a bond, $-O-$, $-C(O)-$, $-C(O)-N(H)-$, $-N(H)-C(O)-$ or $-S(O)_2-$,

R14 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-carbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonyl or 1-4C-alkyl-carbonylamino,

m is an integer from 1 to 4,

n is an integer from 1 to 4,

p is an integer from 1 to 4,

q is an integer from 1 to 4,
and the salts of these compounds.

1-4C-Alkyl is a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

1-4C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Alkoxy radicals having 1 to 4 carbon atoms which may be mentioned in this context are, for example, the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals.

1-8C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 8 carbon atoms. Alkoxy radicals having 1 to 8 carbon atoms which may be mentioned in this context are, for example, the octyloxy, heptyloxy, isoheptyloxy (5-methylhexyloxy), hexyloxy, isoheptyloxy (4-methylpentyloxy), neohexyloxy (3,3-dimethylbutoxy), pentyloxy, isopentyloxy (3-methylbutoxy), neopentyloxy (2,2-dimethylpropoxy), butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy, ethoxy and methoxy radicals.

3-7C-Cycloalkoxy stands for cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy or cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C-Cycloalkylmethoxy stands for cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy or cycloheptylmethoxy, of which cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy are preferred.

3-5C-Cycloalkoxy stands for cyclopropyloxy, cyclobutyloxy and cyclopentyloxy.

3-5C-Cycloalkylmethoxy stands for cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy.

1-4C-Alkoxy which is completely or predominantly substituted by fluorine is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy radical, of which the difluoromethoxy radical is preferred. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy group are replaced by fluorine atoms.

As spiro-linked 5-, 6- or 7-membered hydrocarbon rings, optionally interrupted by an oxygen or sulphur atom, may be mentioned the cyclopentane, cyclohexane, cycloheptane, tetrahydrofuran, tetrahydropyran and the tetrahydrothiophen ring.

3-7C-Cycloalkyl stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

3-7C-Cycloalkylmethyl stands for a methyl radical, which is substituted by one of the abovementioned 3-7C-cycloalkyl radicals. Preferred examples which may be mentioned are the cyclopropylmethyl, the cyclobutylmethyl and the cyclopentylmethyl radicals.

An hydroxy-2-4C-alkoxy radical is, for example 2-hydroxyethoxy.

1-4C-Alkoxy-1-4C-alkoxy stands for one of the abovementioned 1-4C-alkoxy radicals which is substituted by the same or another of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the 2-(methoxy)ethoxy $[-O-CH_2-CH_2-O-CH_3]$ and the 2-(ethoxy)ethoxy radical $[-O-CH_2-CH_2-O-CH_2-CH_3]$.

1-4C-Alkoxy carbonyl is a carbonyl group to which one of the abovementioned 1-4C-alkoxy radicals is bonded. Examples which may be mentioned are the methoxycarbonyl $[CH_3O-C(O)-]$ and the ethoxycarbonyl $[CH_3CH_2O-C(O)-]$ radical.

1-4C-Alkyl carbonyl is a carbonyl group to which one of the abovementioned 1-4C-alkyl radicals is bonded. An example is the acetyl radical $[CH_3C(O)-]$.

An 1-4C-Alkyl carbonylamino radical is, for example, the propionylamino $[C_3H_7C(O)NH-]$ and the acetyl amino radical $[CH_3C(O)NH-]$.

Mono- or Di-1-4C-alkylamino radicals contain in addition to the nitrogen atom, one or two of the abovementioned 1-4C-alkyl radicals. Preferred are the di-1-4C-alkylamino radicals, especially the dimethylamino, the diethylamino and the diisopropylamino radical.

Mono- or Di-1-4C-alkylaminocarbonyl radicals contain in addition to the carbonyl group one of the abovementioned mono- or di-1-4C-alkylamino radicals. Examples which may be mentioned are the N-methyl-, the N,N-dimethyl-, the N-ethyl-, the N-propyl-, the N,N-diethyl- and the N-isopropylaminocarbonyl radical.

Suitable salts for compounds of the formula 1 are all acid addition salts. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids customarily used in pharmacy. Those suitable are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids

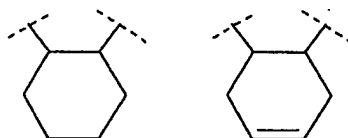
being employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

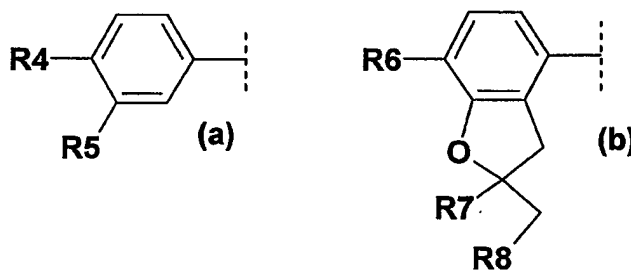
According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula 1 as well as all solvates and in particular all hydrates of the salts of the compounds of formula 1.

Compounds of formula 1 to be emphasized are those in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofurane or tetrahydropyran ring,

R9 is $-(CH_2)_m-S(O)_2-R10$, $-(CH_2)_n-C(O)-R11$ or $-(CH_2)_p-Z-(CH_2)_q-R14$,

R10 is $-N(R12)R13$,

R11 is -N(R12)R13,

R12 and R13 are independent from each other hydrogen or 1-4C-alkyl, or R12 and R13 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl- or a 1-hexahydroazepinylring,

Z represents a bond, -O- or -S(O)₂-,

R14 is hydrogen, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxycarbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl or 1-4C-alkylcarbonylamino,

n is 1 or 2,

m is 1 or 2,

p is 1, 2 or 3,

q is 1 or 2,

and the salts of these compounds.

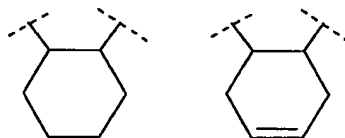
Compounds of formula 1 particularly to be emphasized are those, in which either

R1 is hydrogen and

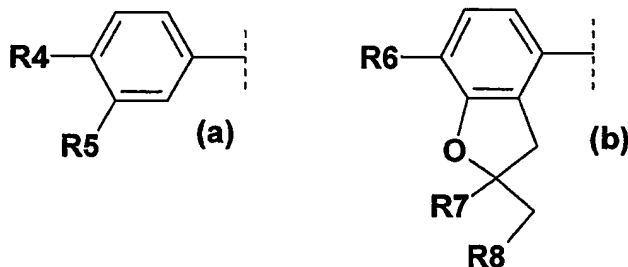
R2 is hydrogen,

or

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy,

R7 is methyl and

R8 is hydrogen,

- 7 -

R9 is $-(CH_2)_m-S(O)_2-R10$, $-(CH_2)_n-C(O)-R11$ or $-(CH_2)_p-Z-(CH_2)_q-R14$,

R10 is $-N(R12)R13$,

R11 is $-N(R12)R13$,

R12 and R13 are independent from each other hydrogen or 1-4C-alkyl, or R12 and R13 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl- or a 1-hexahydroazepinylring,

Z represents $-O-$ or $-S(O)_2-$,

R14 is hydrogen, 1-4C-alkoxy or 1-4C-alkoxy-1-4C-alkoxy,

n is 1 or 2,

m is 1 or 2,

p is 1, 2 or 3,

q is 1 or 2,

and the salts of these compounds.

Preferred compounds of formula 1 are those in which

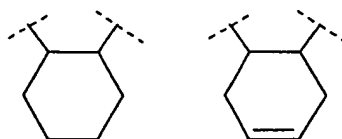
either

R1 is hydrogen and

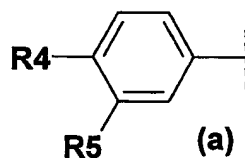
R2 is hydrogen,

or

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formula (a)



wherein

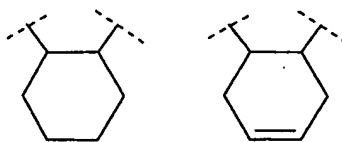
R4 is methoxy,

R5 is methoxy,

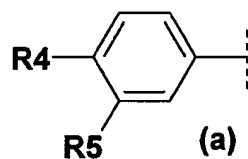
R9 is dimethylaminocarbonylmethyl, aminocarbonylmethyl, piperidin-1-ylcarbonylmethyl or morpholino-4-ylcarbonylmethyl,

and the salts of these compounds.

Particularly preferred compounds of formula 1 are those in which R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formula (a)



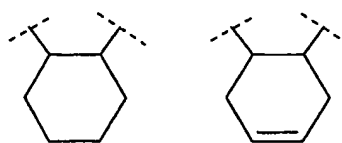
wherein

R4 is methoxy,

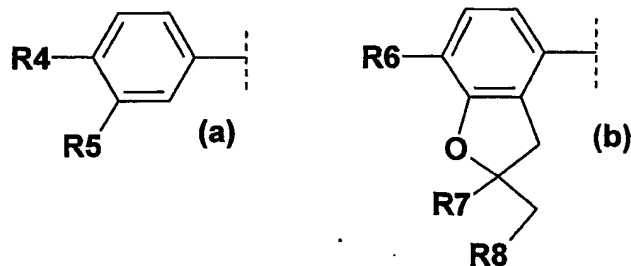
R5 is methoxy,

R9 is aminocarbonylmethyl or isopropylaminocarbonylmethyl,
and the salts of these compounds.

An embodiment (embodiment A) of the compounds of formula 1 are those, in which R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is $-(CH_2)_m-S(O)_2-R_{10}$,

R10 is $-N(R_{12})R_{13}$,

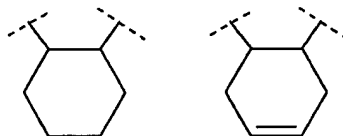
R12 and R13 are independent from each other hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkylmethyl, or R12 and R13 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl- or a 1-hexahydroazepinylring,

m is an integer from 1 to 4,

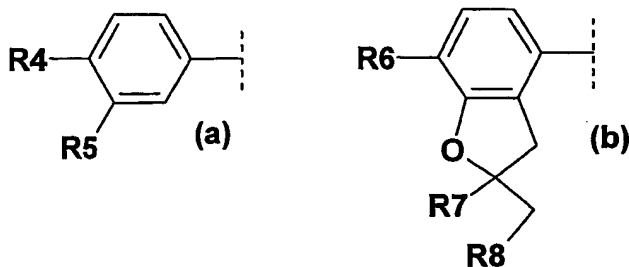
and the salts of these compounds.

Compounds of formula 1 of embodiment A to be emphasized are those in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

- 10 -

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofuran or tetrahydropyran ring,

R9 is $-(CH_2)_m-S(O)_2-R_{10}$,

R10 is $-N(R_{12})R_{13}$,

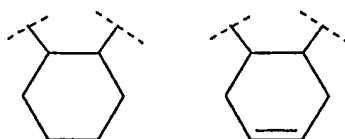
R12 and R13 are independent from each other hydrogen or 1-4C-alkyl, or R12 and R13 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl- or a 1-hexahydroazepinylring,

m is 1 or 2,

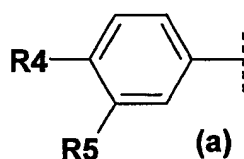
and the salts of these compounds.

Compounds of formula 1 of embodiment A particularly to be emphasized are those, in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formula (a)



wherein

R4 is 1-4C-alkoxy,

R5 is 1-4C-alkoxy,

R9 is $-(CH_2)_m-S(O)_2-R_{10}$,

R10 is $-N(R_{12})R_{13}$,

R12 is hydrogen and

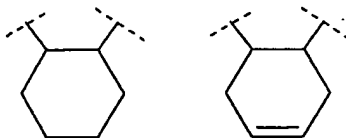
R13 is hydrogen or 1-4C-alkyl,

m is 1 or 2,

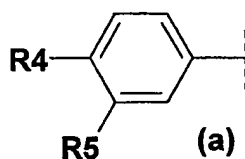
and the salts of these compounds.

Preferred compounds of formula 1 of embodiment A are those, in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formula (a)



wherein

R4 is methoxy,

R5 is methoxy,

R9 is $-(CH_2)_m-S(O)_2-R_{10}$,

R10 is $-N(R_{12})R_{13}$,

R12 is hydrogen and

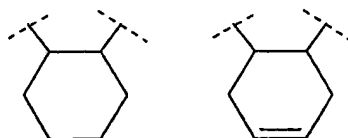
R13 is hydrogen or 1-4C-alkyl,

m is 1,

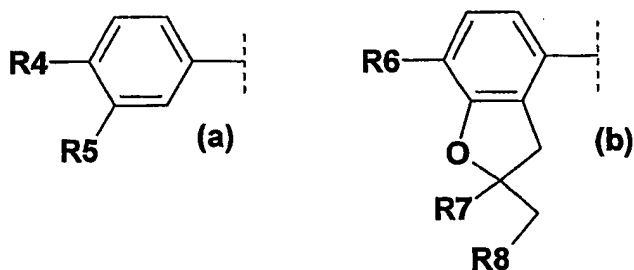
and the salts of these compounds.

Another embodiment (embodiment B) of the compounds of formula 1 are those, in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is $-(CH_2)_n-C(O)-R_{11}$,

R11 is $-N(R_{12})R_{13}$,

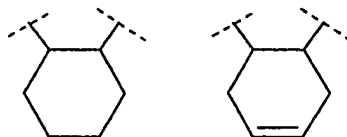
R12 and R13 are independent from each other hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkylmethyl, or R12 and R13 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl- or a 1-hexahydroazepinylring,

n is an integer from 1 to 4,

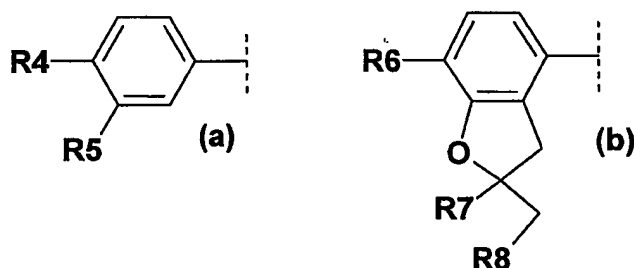
and the salts of these compounds.

Compounds of formula 1 of embodiment B to be emphasized are those in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofurane or tetrahydropyran ring,

R9 is $-(CH_2)_n-C(O)-R_{11}$,

R11 is $-N(R_{12})R_{13}$,

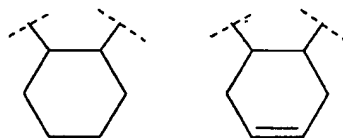
R12 and R13 are independent from each other hydrogen or 1-4C-alkyl, or R12 and R13 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl- or a 1-hexahydroazepinylring,

n is 1 or 2,

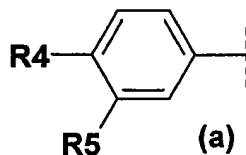
and the salts of these compounds.

Compounds of formula 1 of embodiment B particularly to be emphasized are those, in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formula (a)



wherein

R4 is 1-4C-alkoxy,

R5 is 1-4C-alkoxy,

R9 is $-(CH_2)_n-C(O)-R_{11}$,

R11 is $-N(R_{12})R_{13}$,

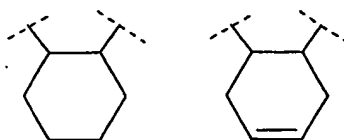
R12 is hydrogen and

R13 is hydrogen or 1-4C-alkyl,

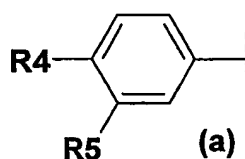
n is 1 or 2,

and the salts of these compounds.

Preferred compounds of formula 1 of embodiment B are those, in which R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



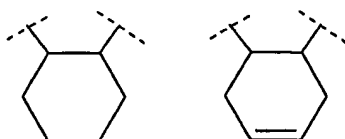
R3 represents a phenyl derivative of formula (a)



wherein

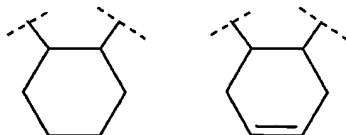
R4 is methoxy,
 R5 is methoxy,
 R9 is $-(CH_2)_n-C(O)-R11$,
 R11 is $-N(R12)R13$,
 R12 is hydrogen and
 R13 is hydrogen or isopropyl,
 m is 1,
 and the salts of these compounds.

A special embodiment of the compounds of the present invention include those compounds of formula 1 in which R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



and R3 represents a phenyl derivative of formula (a).

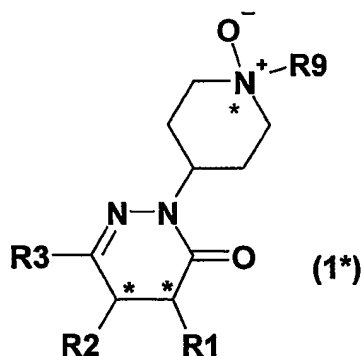
Another special embodiment of the compounds of the present invention include those compounds of formula 1 in which R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formula (a), wherein R4 and R5 stands for methoxy.

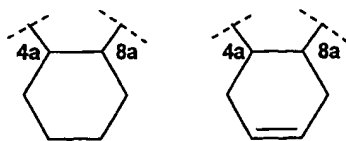
The compounds of formula 1 are chiral compounds with - depending on the meaning of R3 - a chiral center in the phenyl derivative of formula (b), if the substituents -R7 and -CH₂R8 are not identical. However, preferred are those compounds, in which the substituents -R7 and -CH₂R8 are identical or together and with inclusion of the carbon atoms to which they are bonded form a spiro-connected 5-, 6- or 7-membered hydrocarbon ring.

Further possible chiral centers in the compounds of formula 1 are marked in the following formula 1* with an asterix (*):



The invention includes all conceivable pure stereoisomers, as well as all mixtures thereof independent from the ratio, including the racemates.

In those cases, wherein R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from

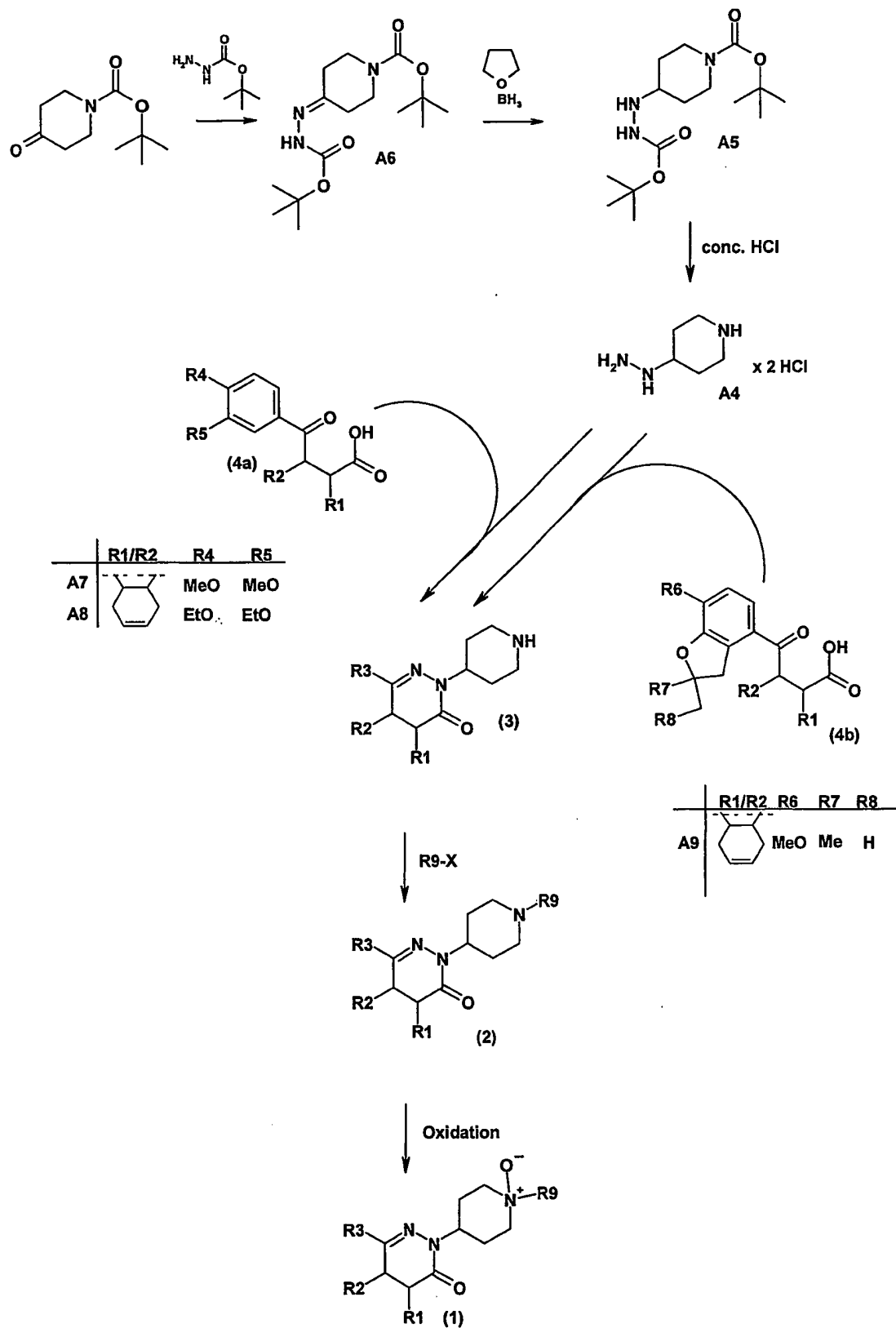


those compounds are preferred, in which the hydrogen atoms in the positions 4a and 8a are cis-configured. Especially preferred in this connection are those compounds, in which the absolute configuration (according to the rules of Cahn, Ingold and Prelog) is S in the position 4a and R in the position 8a.

(4a,8a)-cis-Racemates can be split up into the corresponding enantiomers by methods known by a person skilled in the art. Preferably the racemic mixtures are separated into two diastereomers during the preparation with the help of an optical active separation agent on the stage of the cyclohexanecarboxylic acids or the 1,2,3,6-tetrahydrobenzoic acids (for example starting compounds A1 and A2). As separation agents may be mentioned, for example, optical active amines such as the (+)- and (-)-forms of 1-phenylethylamine [(R)-(+)-1-phenylethylamine = D- α -methylbenzylamine or (S)-(-)-1-phenylethylamine = L- α -methylbenzylamine) and ephedrine, the optical active alkaloids quinine, cinchonine, cinchonidine and brucine.

The compounds according to the invention can be prepared, for example, as described in Reaction scheme 1.

Reaction scheme 1:



Reaction scheme 1 shows that the compounds of formula 1 can be, for example, prepared starting from 4-oxo-piperidine-1-carboxylic acid tert-butyl ester which is reacted in a first reaction step with tert-butylcarbазate to give 4-(tert-Butoxycarbonyl-hydrazono)-piperidine-1-carboxylic acid tert-butyl ester (starting compound A6). Compound A6 is reduced with, for example, the boran tetrahydrofurane complex to give 4-(N'-tert-Butoxycarbonyl-hydrazino)-piperidine-1-carboxylic acid tert-butyl ester (starting compound A5). Treatment of compound A5 with concentrated hydrochloric acid results in the formation of piperidin-4-yl-hydrazine dihydrochloride (starting compound A4).

The reaction of piperidin-4-yl-hydrazine dihydrochloride with benzoyl-1,2,3,6-tetrahydrobenzoic acids or benzoyl-1,2,3,4,5,6-hexahydrobenzoic acids of formulae 4a or 4b leads to the piperidino derivatives of formula 3.

These are reacted with compounds of formula R9-X, wherein X represents a suitable leaving group, preferably a chlorine atom, to give the compounds of formula 2.

In the final reaction step the compounds of formula 2 are oxidized to give the N-oxides of formula 1. The N-oxidation is carried out, for example, with the aid of hydrogen peroxide in methanol or with the aid of m-chloroperoxybenzoic acid in dichloromethane. The person skilled in the art is familiar on the basis of his/her expert knowledge with the reaction conditions necessary for carrying out the N-oxidation.

Suitably, the conversions are carried out analogous to methods which are familiar per se to the person skilled in the art, for example, in the manner which is described in the following examples.

The preparation of benzoyl-1,2,3,6-tetrahydrobenzoic acids or benzoyl-1,2,3,4,5,6-hexahydrobenzoic acids of formulae 4a or 4b is described, for example, in WO98/31674, WO99/31090 and WO99/47505.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallising the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (for example a ketone like acetone, methylethylketone, or methylisobutylketone, an ether, like diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol, such as ethanol, isopropanol) which contains the desired acid, or to which the desired acid is then added. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification into the free compounds which, in turn, can be converted into salts. In this manner, pharmacologically non-tolerable salts can be converted into pharmacologically tolerable salts.

The following examples illustrate the invention in greater detail, without restricting it. As well, further compounds of formula 1, of which the preparation is explicitly not described, can be prepared in an analogous way or in a way which is known by a person skilled in the art using customary preparation methods.

The compounds, which are mentioned in the examples as well as their salts are preferred compounds of the invention.

In the examples, RT stands for room temperature, h for hour(s), min for minute(s) and M. p. for melting point.

ExamplesFinal product

1. 2-{4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-1-oxy-piperidin-1-yl}-acetamide

A solution of 1.2 g of starting compound A10 in 100ml of dichloromethane is washed with an aqueous saturated solution of sodium bicarbonate. Next the solution is dried over magnesium sulfate and cooled to 0 °C. To this solution, 0.6 g of 3-chloroperbenzoic acid (70%) was added. After stirring for 60 min, the mixture is washed with an aqueous saturated solution of sodium bicarbonate, dried over magnesium sulfate and evaporated. The residue is crystallised from ethyl acetate. M. p. 159-161°C

2. 2-{4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-1-oxy-piperidin-1-yl}-N-isopropyl-acetamide

Prepared from 2-{4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl}-N-isopropyl-acetamide (A11) as described for final product 1. M.p. 130-132°C

3. 2-{4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,6,7,8,8a-hexahydro-1H-phthalazin-2-yl]-1-oxy-piperidin-1-yl}-acetamide

Prepared from 2-{4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,6,7,8,8a-hexahydro-1H-phthalazin-2-yl]-piperidin-1-yl}-acetamide (A12) as described for final product 1. M.p. 176-177°C

Starting Compounds**A1. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-piperidin-4-yl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride**

A solution of 50 mmol of the salt of (S)-(-)- α -methylbenzylamine and (cis)-2-(3,4-dimethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid (starting compound A8), 55 mmol of piperidin-4-yl-hydrazine dihydrochloride and 100 mmol of triethylamine in 150 ml of 1-propanol is refluxed for 18 h. After cooling to RT, the precipitate is filtered off and dried. M. p. 285-288°C

A2. (4aS,8aR)-4-(3,4-Diethoxy-phenyl)-2-piperidin-4-yl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride

Prepared from the salt of (S)-(-)- α -methylbenzylamine and (cis)-2-(3,4-diethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid (starting compound A9) in 2-propanol as described for compound A1.
M. p. 248-250°C

A3. (cis)-4-(7-Methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-2-piperidin-4-yl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride

Prepared from (cis)-2-(2,3-Dihydro-2,2-dimethyl-7-methoxybenzofuran-4 carbonyl)-1,2,3,6-tetrahydrobenzoic acid (starting compound A10) in 1-propanol as described for compound A1. After evaporating the solvent, the residue is partitioned between dichloromethane and aqueous sodium carbonate. The dichloromethane layer is dried over magnesium sulfate and evaporated. The residue is dissolved in dichloromethane and after the addition of a solution of hydrochloric acid in ether, the compound precipitates. M. p. 288-290°C

A4. Piperidin-4-yl-hydrazine dihydrochloride

A mixture of 0.1 mole of 4-(N'-tert-Butoxycarbonyl-hydrazino)-piperidine-1-carboxylic acid tert-butyl ester (starting compound A6) and 150 ml of concentrated hydrochloric acid is heated at 90°C for 60 min after which the clear solution is evaporated. The residue is washed with tetrahydrofurane, filtered off and dried under vacuum. M. p. 256-259°C

A5. 4-(N'-tert-Butoxycarbonyl-hydrazino)-piperidine-1-carboxylic acid tert-butyl ester

150 ml of a solution of borohydride in tetrahydrofurane (1.0 mol/l) is slowly added to a solution of 0.12 mole of 4-(tert-Butoxycarbonyl-hydrazono)-piperidine-1-carboxylic acid tert-butyl ester (starting compound A7) in 100 ml of dry tetrahydrofurane. After complete addition, the mixture is stirred for another 30 min after which a 100 ml of water is added to destroy the excess of borohydride. Subsequently the

tetrahydrofuran is evaporated and the resulting aqueous solution extracted with diethyl ether. After drying the solvent over magnesium sulfate, the ether is evaporated. M. p. 112-115°C

A6. 4-(tert-Butoxycarbonyl-hydrazono)-piperidine-1-carboxylic acid tert-butyl ester

A mixture of 0.15 mole of 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (commercially available) and 0.15 mole of tert-butylcarbazate in 250 ml of hexane is stirred for 18 h at RT. The precipitate is filtered off and dried under vacuum. M. p. 172-174°C

A7. (cis)-2-(3,4-Dimethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid

Prepared as described in WO98/31674.

A8. (cis)-2-(3,4-diethoxybenzoyl)-1,2,3,6-tetrahydrobenzoic acid

Prepared as described in WO99/47505.

A9. (cis)-2-(2,3-Dihydro-2,2-dimethyl-7-methoxybenzofuran-4-carbonyl)-1,2,3,6-tetrahydro-benzoic acid

Prepared as described in WO99/31090.

A10. 2-{4-[(4aS,8aR)-4-(3,4-Dimethoxyphenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl}-2H-acetamide hydrochloride

A mixture of 2.0 g of (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-piperidin-4-yl-4a,5,8,8a-tetrahydro-2H-phthalazin-1-one hydrochloride (starting compound A1), 1.0 g of 2-chloroacetamide and 2.0 g of potassium carbonate in 20 ml of dimethylformamide is stirred for 18 h at RT after which 100 ml of water is added to the reaction mixture. The mixture is extracted with diethyl ether, the ether solution dried over magnesium sulfate and evaporated. The residue is dissolved in ethanol and after the addition of a saturated solution of hydrochloric acid in ether, the title compound precipitates. M. p. 241-243 °C.

A11. 2-{4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,8,8a-tetrahydro-1H-phthalazin-2-yl]-piperidin-1-yl}-N-isopropyl-acetamide

Prepared as described in WO02/064584.

A12. 2-[4-[(4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-1-oxo-4a,5,6,7,8,8a-hexahydro-1H-phthalazin-2-yl]-piperidin-1-yl]-acetamide hydrochloride

Prepared from A13 and chloroacetamide as described for A10. M. p. 201-203°C.

A13. (4aS,8aR)-4-(3,4-Dimethoxy-phenyl)-2-piperidin-4-yl-4a,5,6,7,8,8a-hexahydro-2H-phthalazin-1-one hydrochloride

A solution of 50 mmol of A14 in dichloromethane is washed twice with 1N sulphuric acid, dried over magnesium sulphate and evaporated. The residue is dissolved in 150 ml of ethyl acetate, 50 mmol of 4-hydrazinopiperidine dihydrochloride and 75 mmol of triethylamine is added and the resulting mixture is refluxed for 18 h. After cooling to RT, the precipitate is filtered off and dried. M. p. 291-293 °C (with decomposition).

A14. L-(-)- α -methylbenzylamine salt of (1R,2S)-2-[1-(3,4-Dimethoxy-phenyl)-methanoyl]-cyclohexanecarboxylic acid

A solution of 0.25 mole of L-(-)- α -methylbenzylamine in 100 ml of ethyl acetate is added to a solution of 0.5 mole of 2-[1-(3,4-Dimethoxy-phenyl)-methanoyl]-cyclohexanecarboxylic acid in 1.5 l of ethyl acetate. The resulting mixture is filtered off and suspended in 1 l of ethyl acetate, heated for 1 h at 60°C and filtered off while still warm. M.p. 155-157 °C

Commercial utility

The compounds according to the invention have useful pharmacological properties which make them industrially utilizable. As selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4), they are suitable on the one hand as bronchial therapeutics (for the treatment of airway obstructions on account of their dilating action but also on account of their respiratory rate- or respiratory drive-increasing action) and for the removal of erectile dysfunction on account of their vascular dilating action, but on the other hand especially for the treatment of disorders, in particular of an inflammatory nature, e.g. of the airways (asthma prophylaxis), of the skin, of the intestine, of the eyes, of the CNS and of the joints, which are mediated by mediators such as histamine, PAF (platelet-activating factor), arachidonic acid derivatives such as leukotrienes and prostaglandins, cytokines, interleukins, chemokines, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) or oxygen free radicals and proteases. In this context, the compounds according to the invention are distinguished by a low toxicity, a good enteral absorption (high bioavailability), a large therapeutic breadth and the absence of significant side effects.

On account of their PDE-inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine as therapeutics, where they can be used, for example, for the treatment and prophylaxis of the following illnesses: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of varying origin (bronchitis, allergic bronchitis, bronchial asthma, emphysema, COPD); dermatoses (especially of proliferative, inflammatory and allergic type) such as psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, Lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and widespread pyodermias, endogenous and exogenous acne, acne rosacea and other proliferative, inflammatory and allergic skin disorders; disorders which are based on an excessive release of TNF and leukotrienes, for example disorders of the arthritis type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic conditions), disorders of the immune system (AIDS, multiple sclerosis), graft versus host reaction, allograft rejections, types of shock (septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)) and also generalized inflammations in the gastrointestinal region (Crohn's disease and ulcerative colitis); disorders which are based on allergic and/or chronic, immunological false reactions in the region of the upper airways (pharynx, nose) and the adjacent regions (paranasal sinuses, eyes), such as allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and also nasal polyps; but also disorders of the heart which can be treated by PDE inhibitors, such as cardiac insufficiency, or disorders which can be treated on account of the tissue-relaxant action of the PDE inhibitors, such as, for example, erectile dysfunction or colics of the kidneys and of the ureters in connection with kidney stones. In addition, the compounds of the invention are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile dementia (Alz-

heimer's disease), memory impairment associated with Parkinson's disease or multiinfarct dementia; and also illnesses of the central nervous system, such as depressions or arteriosclerotic dementia.

The invention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the above mentioned illnesses. The method is characterized in that a therapeutically active and pharmacologically effective and tolerable amount of one or more of the compounds according to the invention is administered to the ill mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention furthermore relates to pharmaceutical compositions for the treatment and/or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the invention.

Additionally, the invention relates to an article of manufacture, which comprises packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for antagonizing the effects of the cyclic nucleotide phosphodiesterase of type 4 (PDE4), ameliorating the symptoms of an PDE4-mediated disorder, and wherein the packaging material comprises a label or package insert which indicates that the pharmaceutical agent is useful for preventing or treating PDE4-mediated disorders, and wherein said pharmaceutical agent comprises one or more compounds of formula 1 according to the invention. The packaging material, label and package insert otherwise parallel or resemble what is generally regarded as standard packaging material, labels and package inserts for pharmaceuticals having related utilities.

The pharmaceutical compositions are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries or excipients which are suitable for the desired pharmaceutical formulations on account of his/her expert knowledge. In addition to solvents, gel for-

mers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

The administration of the pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral delivery is preferred.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation in the form of an aerosol; the aerosol particles of solid, liquid or mixed composition preferably having a diameter of 0.5 to 10 μm , advantageously of 2 to 6 μm .

Aerosol generation can be carried out, for example, by pressure-driven jet atomizers or ultrasonic atomizers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

Depending on the inhaler system used, in addition to the active compounds the administration forms additionally contain the required excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of apparatuses are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is as right as possible for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application EP 0 505 321), using which an optimal administration of active compound can be achieved.

For the treatment of dermatoses, the compounds according to the invention are in particular administered in the form of those pharmaceutical compositions which are suitable for topical application. For the production of the pharmaceutical compositions, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The pharmaceutical compositions according to the invention are prepared by processes known per se. The dosage of the active compounds is carried out in the order of magnitude customary for PDE inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the

active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhalation is customarily between 0.1 and 3 mg per day. The customary dose in the case of systemic therapy (p.o. or i.v.) is between 0.03 and 3 mg/kg per day.

Biological investigations

The second messenger cyclic AMP (cAMP) is well-known for inhibiting inflammatory and immunocompetent cells. The PDE4 isoenzyme is broadly expressed in cells involved in the initiation and propagation of inflammatory diseases (H Tenor and C Schudt, in „Phosphodiesterase Inhibitors“, 21-40, „The Handbook of Immunopharmacology“, Academic Press, 1996), and its inhibition leads to an increase of the intracellular cAMP concentration and thus to the inhibition of cellular activation (JE Souness et al., Immunopharmacology 47: 127-162, 2000).

The antiinflammatory potential of PDE4 inhibitors in vivo in various animal models has been described (MM Teixeira, TIPS 18: 164-170, 1997). For the investigation of PDE4 inhibition on the cellular level (in vitro), a large variety of proinflammatory responses can be measured. Examples are the superoxide production of neutrophilic (C Schudt et al., Arch Pharmacol 344: 682-690, 1991) or eosinophilic (A Hatzelmann et al., Brit J Pharmacol 114: 821-831, 1995) granulocytes, which can be measured as luminol-enhanced chemiluminescence, or the synthesis of tumor necrosis factor- α in monocytes, macrophages or dendritic cells (Gantner et al., Brit J Pharmacol 121: 221-231, 1997, and Pulmonary Pharmacol Therap 12: 377-386, 1999). In addition, the immunomodulatory potential of PDE4 inhibitors is evident from the inhibition of T-cell responses like cytokine synthesis or proliferation (DM Essayan, Biochem Pharmacol 57: 965-973, 1999). Substances which inhibit the secretion of the afore-mentioned proinflammatory mediators are those which inhibit PDE4. PDE4 inhibition by the compounds according to the invention is thus a central indicator for the suppression of inflammatory processes.

Method for measuring inhibition of PDE4 activity

PDE4 activity was determined as described by Thompson et al. (Adv Cycl Nucl Res 10: 69-92, 1979) with some modifications (Bauer and Schwabe, Naunyn-Schmiedeberg's Arch Pharmacol 311: 193-198, 1980). At a final assay volume of 200 μ l (96well microtiter plates) the assay mixture contained 20 mM Tris (pH 7.4), 5 mM $MgCl_2$, 0.5 μ M cAMP, [3H]cAMP (about 30,000 cpm/assay), the test compound and an aliquot of cytosol from human neutrophils which mainly contains PDE4 activity as described by Schudt et al. (Naunyn-Schmiedeberg's Arch Pharmacol 344: 682-690, 1991); the PDE3-specific inhibitor Motapizone (1 μ M) was included to suppress PDE3 activity originating from contaminating platelets. Serial dilutions of the compounds were prepared in DMSO and further diluted 1:100 (v/v) in the assays to obtain the desired final concentrations of the inhibitors at a DMSO concentration of 1 % (v/v) which by itself only slightly affected PDE4 activity.

After preincubation for 5 min at 37°C, the reaction was started by the addition of substrate (cAMP) and the assays were incubated for further 15 min at 37°C. 50 μ l of 0.2 N HCl was added to stop the reaction and the assays were left on ice for about 10 min. Following incubation with 25 μ g 5'-nucleotidase (Crotalus atrox snake venom) for 10 min at 37°C, the assays were loaded on QAE Sephadex A-25 (1 ml bed

volume). The columns were eluted with 2 ml of 30 mM ammonium formate (pH 6.0) and the eluate was counted for radioactivity. Results were corrected for blank values (measured in the presence of denatured protein) which were below 5 % of total radioactivity. The amount of cyclic nucleotides hydrolyzed did not exceed 30 % of the original substrate concentration. The IC_{50} -values for the compounds according to the invention for the inhibition of the PDE4 activity were determined from the concentration-inhibition curves by nonlinear-regression.

The inhibitory values determined for the compounds according to the invention follow from the following table A, in which the numbers of the compounds correspond to the numbers of the examples.

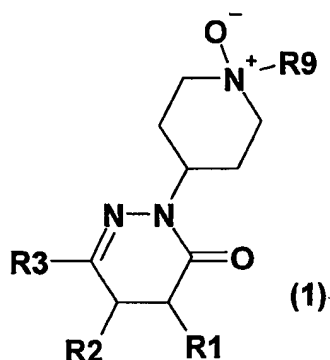
Table A

Inhibition of PDE4 activity [measured as $-\log IC_{50}$ (mol/l)]

compound	$-\log IC_{50}$
1	8.31
2	9.3
3	7.5

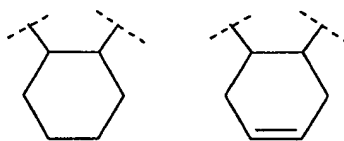
Patent claims

1. Compounds of formula 1,

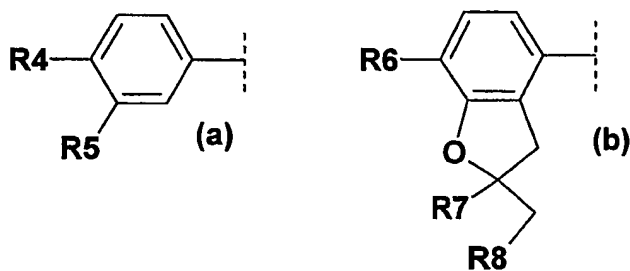


in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
 R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
 R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,
 R7 is 1-4C-alkyl and
 R8 is hydrogen or 1-4C-alkyl,
 or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is $-(CH_2)_m-S(O)_2-R_{10}$, $-(CH_2)_n-C(O)-R_{11}$ or $-(CH_2)_p-Z-(CH_2)_q-R_{14}$,

R10 is $-N(R_{12})R_{13}$,

R11 is $-N(R_{12})R_{13}$,

R12 and R13 are independent from each other hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-methyl, or R12 and R13 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl- or a 1-hexahydroazepinylring,

Z represents a bond, $-O-$, $-C(O)-$, $-C(O)-N(H)-$, $-N(H)-C(O)-$ or $-S(O)_2-$,

R14 is hydrogen, hydroxyl, 1-4C-alkoxy, hydroxy-2-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxy-carbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, 1-4C-alkylcarbonyl or 1-4C-alkyl-carbonylamino,

m is an integer from 1 to 4,

n is an integer from 1 to 4,

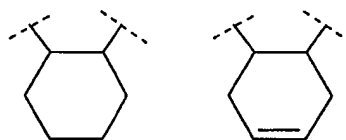
p is an integer from 1 to 4,

q is an integer from 1 to 4,

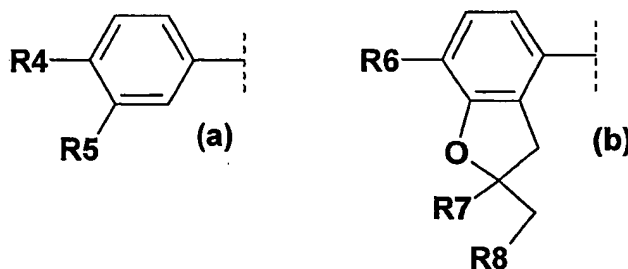
and the salts of these compounds.

2. Compounds of formula 1 according to claim 1, in which

R1 and R2 represent independently from one another hydrogen or 1-4C-alkyl, or R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofurane or tetrahydropyran ring,

R9 is $-(CH_2)_m-S(O)_2-R10$, $-(CH_2)_n-C(O)-R11$ or $-(CH_2)_p-Z-(CH_2)_q-R14$,

R10 is $-N(R12)R13$,

R11 is $-N(R12)R13$,

R12 and R13 are independent from each other hydrogen or 1-4C-alkyl, or R12 and R13 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl- or a 1-hexahydroazepinylring,

Z represents a bond, $-O-$ or $-S(O)_2-$,

R14 is hydrogen, 1-4C-alkoxy, 1-4C-alkoxy-1-4C-alkoxy, 1-4C-alkoxycarbonyl, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl or 1-4C-alkylcarbonylamino,

n is 1 or 2,

m is 1 or 2,

p is 1, 2 or 3,

q is 1 or 2,

and the salts of these compounds.

3. Compounds of formula 1 according to claim 1, in which

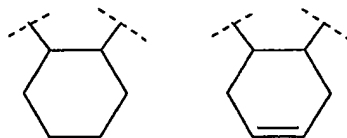
either

R1 is hydrogen and

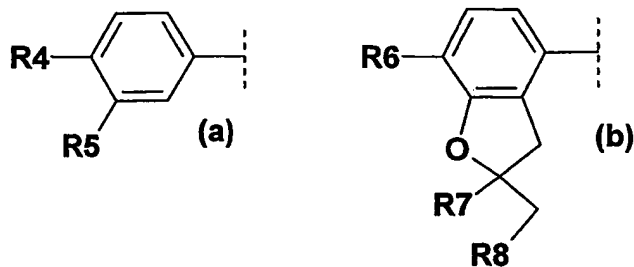
R2 is hydrogen,

or

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy,

R7 is methyl and

R8 is hydrogen,

R9 is $-(CH_2)_m-S(O)_2-R_{10}$, $-(CH_2)_n-C(O)-R_{11}$ or $-(CH_2)_p-Z-(CH_2)_q-R_{14}$,

R10 is $-N(R_{12})R_{13}$,

R11 is $-N(R_{12})R_{13}$,

R12 and R13 are independent from each other hydrogen or 1-4C-alkyl, or R12 and R13 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl- or a 1-hexahydroazepinyling,

Z represents $-O-$ or $-S(O)_2-$,

R14 is hydrogen, 1-4C-alkoxy or 1-4C-alkoxy-1-4C-alkoxy,

n is 1 or 2,

m is 1 or 2,

p is 1, 2 or 3,

q is 1 or 2,

and the salts of these compounds.

4. Compounds of formula 1 according to claim 1, in which

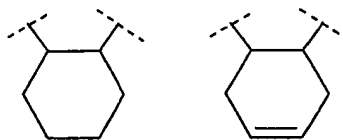
either

R1 is hydrogen and

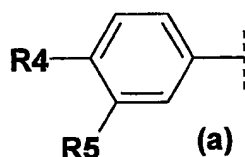
R2 is hydrogen,

or

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formula (a)



wherein

R4 is methoxy,

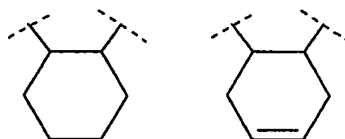
R5 is methoxy,

R9 is dimethylaminocarbonylmethyl, aminocarbonylmethyl, piperidin-1-ylcarbonylmethyl or morpholino-4-ylcarbonylmethyl,

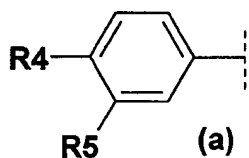
and the salts of these compounds.

5. Compounds of formula 1 according to claim 1, in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formula (a)



wherein

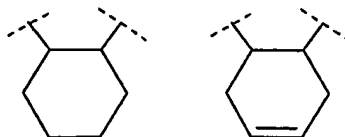
R4 is methoxy,

R5 is methoxy,

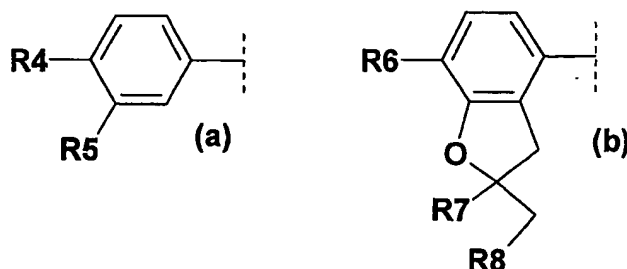
R9 is aminocarbonylmethyl or isopropylaminocarbonylmethyl, and the salts of these compounds.

6. Compounds of formula 1 according to claim 1, in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-8C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R6 is 1-4C-alkoxy, 3-5C-cycloalkoxy, 3-5C-cycloalkylmethoxy, or 1-4C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is 1-4C-alkyl and

R8 is hydrogen or 1-4C-alkyl,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked 5-, 6- or 7-membered hydrocarbon ring, optionally interrupted by an oxygen or sulphur atom,

R9 is $-(CH_2)_n-C(O)-R_{11}$,

R11 is $-N(R_{12})R_{13}$,

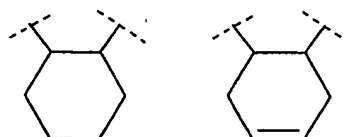
R12 and R13 are independent from each other hydrogen, 1-7C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkylmethyl, or R12 and R13 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl- or a 1-hexahydroazepinylring,

n is an integer from 1 to 4,

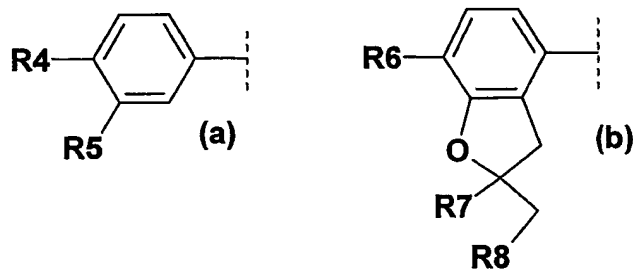
and the salts of these compounds.

7. Compounds of formula 1 according to claim 1, in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



R3 represents a phenyl derivative of formulae (a) or (b)



wherein

R4 is 1-4C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R5 is 1-4C-alkoxy,

R6 is 1-2C-alkoxy or 1-2C-alkoxy which is completely or predominantly substituted by fluorine,

R7 is methyl and

R8 is hydrogen,

or wherein

R7 and R8 together and with inclusion of the two carbon atoms, to which they are bonded, form a spiro-linked cyclopentane, cyclohexane, tetrahydrofurane or tetrahydropyran ring,

R9 is $-(CH_2)_n-C(O)-R11$,

R11 is $-N(R12)R13$,

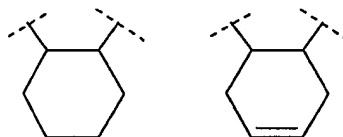
R12 and R13 are independent from each other hydrogen or 1-4C-alkyl, or R12 and R13 together and with inclusion of the nitrogen atom to which they are bonded, form a 4-morpholinyl-, 1-pyrrolidinyl-, 1-piperidinyl- or a 1-hexahydroazepinylring,

n is 1 or 2,

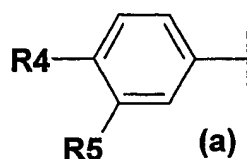
and the salts of these compounds.

8. Compounds of formula 1 according to claim 1, in which

R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



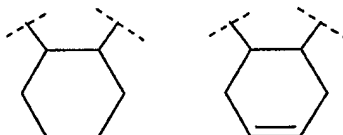
R3 represents a phenyl derivative of formula (a)



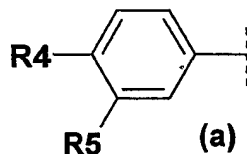
wherein

R4 is 1-4C-alkoxy,
 R5 is 1-4C-alkoxy,
 R9 is $-(CH_2)_n-C(O)-R_{11}$,
 R11 is $-N(R_{12})R_{13}$,
 R12 is hydrogen and
 R13 is hydrogen or 1-4C-alkyl,
 n is 1 or 2,
 and the salts of these compounds.

9. Compounds of formula 1 according to claim 1, in which R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



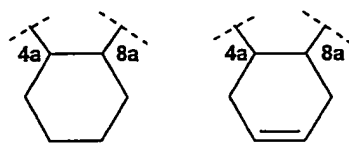
R3 represents a phenyl derivative of formula (a)



wherein

R4 is methoxy,
 R5 is methoxy,
 R9 is $-(CH_2)_n-C(O)-R_{11}$,
 R11 is $-N(R_{12})R_{13}$,
 R12 is hydrogen and
 R13 is hydrogen or isopropyl,
 m is 1,
 and the salts of these compounds.

10. Compounds of formula 1 according to one of the claims 1 to 9 in which R1 and R2 together and with inclusion of the two carbon atoms, to which they are bonded, form a group selected from



and in which the hydrogen atoms in the positions 4a and 8a are cis-configured.

11. Compounds of formula 1 according to claim 10 in which the absolute configuration (according to the rules of Cahn, Ingold and Prelog) is S in the position 4a and R in the position 8a.
12. Compounds of formula 1 according to one of the claims 1 to 4 and 6 to 7 in which R₃ represents a phenyl derivative of formula (a).
13. Compounds of formula 1 according to claim 1 for the treatment of diseases.
14. Pharmaceutical compositions containing one or more compounds of formula 1 according to claim 1 together with the usual pharmaceutical auxiliaries and/or carrier materials.
15. Use of compounds of the formula 1 according to claim 1 for the preparation of pharmaceutical compositions for the treatment of airway disorders.
16. A method for treating an illness treatable by the administration of a PDE4 inhibitor in a patient comprising administering to said patient in need thereof a therapeutically effective amount of a compound of formula 1 as claimed in claim 1.
17. A method for treating airway disorders in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula 1 as claimed in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08676

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/04 C07D405/14 A61K31/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 02 085906 A (ALTANA PHARMA AG) 31 October 2002 (2002-10-31) cited in the application page 31 -page 41; claims 1-13 ---	1-17
P,A	WO 02 064584 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 22 August 2002 (2002-08-22) cited in the application page 25 -page 36; claims 1-13 ---	1-17
Y	WO 99 31090 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 24 June 1999 (1999-06-24) cited in the application page 34 -page 38; claims 1-10 ---	1-17
	--- -/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

24 November 2003

Date of mailing of the international search report

12/12/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kyriakakou, G

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08676

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 30777 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 3 May 2001 (2001-05-03) cited in the application page 21 -page 25; claims 1-10 ---	1-17
Y	WO 99 31071 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 24 June 1999 (1999-06-24) cited in the application page 32 -page 36; claims 1-10 ---	1-17
Y	WO 98 31674 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 23 July 1998 (1998-07-23) cited in the application page 49 -page 55; claims 1-10 ---	1-17
Y	WO 93 07146 A (SYNTEX INC.) 15 April 1993 (1993-04-15) cited in the application page 162 -page 169; claims 1-33 ---	1-17
Y	MARGARETHA VAN DER MEY ET AL.: "Novel Selective Phosphodiesterase (PDE4) inhibitors. 4. Resolution, Absolute Configuration and PDE4 Inhibitory Activity of cis-Tetra- and cis-Hexahydrophthalazinones" JOURNAL OF MEDICINAL CHEMISTRY., vol. 45, no. 12, 6 June 2002 (2002-06-06), pages 2526-2533, XP002262562 AMERICAN CHEMICAL SOCIETY., US ISSN: 0022-2623 cited in the application the whole document ---	1-17
Y	MARGARETHA VAN DER MEY ET AL.: "Novel Selective PDE4 Inhibitors.3. In Vivo Antiinflammatory Activity of a New Series of N-Substituted cis-Tetra- and cis-Hexahydrophthalazinones" JOURNAL OF MEDICINAL CHEMISTRY., vol. 45, no. 12, 6 June 2002 (2002-06-06), pages 2520-2525, XP002262563 AMERICAN CHEMICAL SOCIETY., US ISSN: 0022-2623 cited in the application the whole document --- -/--	1-17

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/EP 03/08676

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>MARGARETHA VAN DER MEY ET AL.: "Novel Selective PDE4 Inhibitors. 2. Synthesis and Structure-Activity Relationships of 4-Aryl-Substituted cis-Tetra- and Cis-Hexahydrophthalazinones" JOURNAL OF MEDICINAL CHEMISTRY., vol. 44, no. 16, 2 August 2001 (2001-08-02), pages 2523-2535, XP002222951 AMERICAN CHEMICAL SOCIETY., US ISSN: 0022-2623 cited in the application the whole document</p> <p>-----</p>	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08676

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16 and 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08676

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02085906	A	31-10-2002	WO 02085906 A2	31-10-2002
WO 02064584	A	22-08-2002	CA 2438520 A1	22-08-2002
			EE 200300311 A	15-10-2003
			WO 02064584 A1	22-08-2002
			EP 1362044 A1	19-11-2003
WO 9931090	A	24-06-1999	AU 753576 B2	24-10-2002
			AU 2270199 A	05-07-1999
			CA 2314111 A1	24-06-1999
			EE 200000335 A	15-10-2001
			WO 9931090 A1	24-06-1999
			EP 1042319 A1	11-10-2000
			HU 0004561 A2	28-03-2002
			JP 2002508368 T	19-03-2002
			PL 341239 A1	26-03-2001
			US 6380196 B1	30-04-2002
WO 0130777	A	03-05-2001	AU 1515101 A	08-05-2001
			BR 0014990 A	18-06-2002
			CA 2388119 A1	03-05-2001
			CN 1382137 T	27-11-2002
			CZ 20021457 A3	17-07-2002
			WO 0130777 A1	03-05-2001
			EP 1244654 A1	02-10-2002
			HU 0203487 A2	28-02-2003
			JP 2003512466 T	02-04-2003
			NO 20021959 A	29-05-2002
			SK 7232002 A3	10-09-2002
			TR 200201128 T2	21-08-2002
			US 6544993 B1	08-04-2003
			US 2003166655 A1	04-09-2003
			ZA 200203157 A	10-04-2003
WO 9931071	A	24-06-1999	AU 1760399 A	05-07-1999
			WO 9931071 A1	24-06-1999
WO 9831674	A	23-07-1998	AT 233247 T	15-03-2003
			AU 735934 B2	19-07-2001
			AU 5862998 A	07-08-1998
			BR 9806752 A	14-03-2000
			CN 1127487 B	12-11-2003
			DE 69811645 D1	03-04-2003
			DK 971901 T3	10-06-2003
			EA 2764 B1	29-08-2002
			EE 9900274 A	15-02-2000
			WO 9831674 A1	23-07-1998
			EP 0971901 A1	19-01-2000
			HU 0001541 A2	28-05-2001
			IL 130659 A	25-07-2002
			JP 2001508078 T	19-06-2001
			NO 993301 A	10-09-1999
			NZ 336573 A	27-10-2000
			PL 334561 A1	13-03-2000
			PT 971901 T	31-07-2003
			SI 971901 T1	31-10-2003
			SK 95199 A3	10-12-1999
			TR 9901653 T2	21-10-1999

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9831674 A		US 6103718 A	15-08-2000
WO 9307146 A	15-04-1993	AT 183745 T	15-09-1999
		AU 670544 B2	25-07-1996
		AU 2781592 A	03-05-1993
		CA 2117059 A1	15-04-1993
		DE 69229874 D1	30-09-1999
		DE 69229874 T2	09-12-1999
		DK 612321 T3	13-12-1999
		EP 0612321 A1	31-08-1994
		ES 2105920 A1	16-10-1997
		ES 2135416 T3	01-11-1999
		FI 941567 A	06-04-1994
		GR 3030969 T3	30-11-1999
		HU 66969 A2	30-01-1995
		HU 9500113 A3	28-06-1995
		IL 103388 A	30-09-1997
		JP 3245165 B2	07-01-2002
		JP 7500321 T	12-01-1995
		KR 263494 B1	01-08-2000
		MX 9205794 A1	01-04-1993
		NO 941210 A	05-04-1994
		NZ 244660 A	26-05-1995
		PT 100938 A ,B	29-10-1993
		WO 9307146 A1	15-04-1993
		US 5716954 A	10-02-1998
		ZA 9207755 A	08-04-1994

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.